Claim 1

{Formula I}

[In this formula R^1 represents H or CH_2OR^9, where R^9 represents the {Formula II} given below:

{Formula II}

R^2 represents O=, HO, CH_3COO, C_2H_5 or $R^{10}O$, where R^{10} is given in the Formula III below:

{Formula III}

R^3 represents H, $COCH_3$, R^4 represents CH_3 or C_2H_5 and R^5 represents H or the Formula IV below:

{Formula IV}

where R^{11} represents H or $COCH_3$, R^{12} represents H, $COCH_3$, COC_2H_5, COC_3H_7 or $COCH_2CH(CH_3)_2$, R6 represents H, OH or OCH_3, R7 represents NH_2, $NHCOCF_3$, or Formula IV' below:

{Formula IV'}

and R8 represents H or the Formula V below:

{Formula V}

(19)

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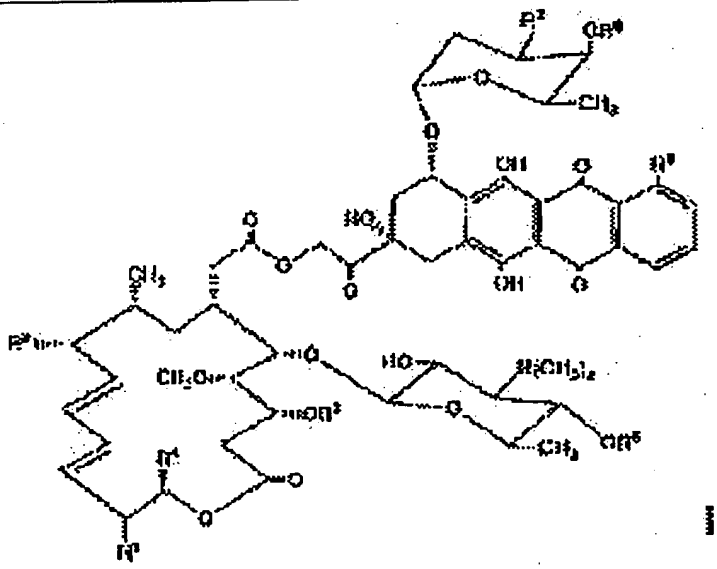
(74) Representative:

(54) ANTHRACYCLINE-MACROLIDE COMPLEX

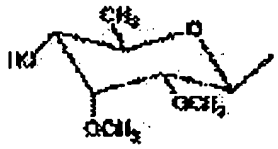
(57) Abstract:

PURPOSE: To obtain the subject new complex effective to lung cancer with few side effects by using a macrolide-based antibiotic as drug carrier to direct anthracycline-based carcinostatic antibiotics toward the lung.

CONSTITUTION: The objective complex of formula I [R1 is H or CH2OR9 (R9 is of formula II); R2 is O=, HO, etc.; R3 is H, COC2H5, etc.; R4 is CH3 or C2H5; R5 is H or of formula III (R11 is H or COCH3; R12 is H, COC3H7, etc.); R6 is H, OH< etc.; R7 is NH2, NHCOCF3, etc.; R8 is H or of formula IV]. It is recommended that this complex be obtained by a process wherein the 7- aldehydemethyl group of the 2-oxo-oxacyclohexadeca-11,13-diene ring of a macrolide antibiotic is oxidized into 7-carboxymethyl group; whereas, the amino group of daunosamine, an anthracycline-based carcinostatic antibiotic, is protected in advance; then, an ester linkage is formed between the 8- hydroxyacetyl group of 5,12-naphthacenedione and the above-mentioned 7- carboxymethyl group.



I



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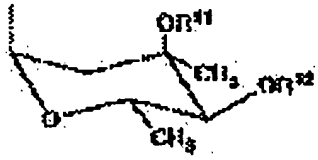
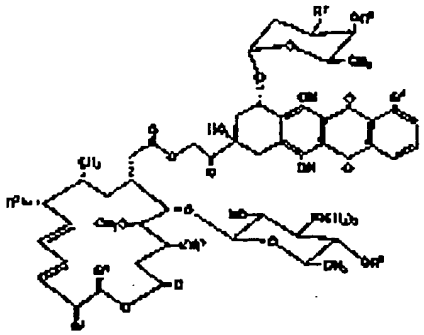


III

IV

CLAIMS

[Claim 1] Anthracycline-macrolide complex shown by the following formula (I).



(I)

[Formula 1]

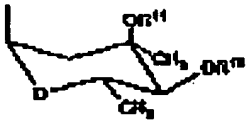
H or CH2 OR9 (however, R9 expresses the following formula (II)) is expressed, and the inside R1 of [Formula 2].

(II)

R2 O=, HO, CH3 COO, C2 H5 COO, or R10O (however, R10 expresses the following formula (III).) is expressed, and it [Formula 3].

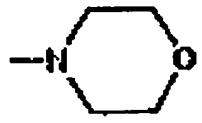
(III)

R3 H and COCH3 Or COC2 H5 It expresses and is R4. CH3 Or C2 H5 It expresses and is R5. H or the following formula (IV) [Formula 4]



(IV)

It means (however, R11 expresses H or COCH3, and R12 expresses H, COCH3, COC2H5, COC3 H7, or COCH2 CH (CH3)2), and is R6. H, OH, or OCH3 It expresses and is R7. NH2 and NHCOCF3 Or [Formula 5]



A ** table is carried out and it is R8. H or the following formula (V)
[Formula 6]

[Claim 4] R1 CH2 OR9 (however, R9 formula (II)) and R2 O=, R3 H and R4 C2 H5 and R5 A formula (IV) (however, R H and R12 H) and R6 OCH3 and R7 NHCOCF3 And R8 Anthracycline-macrolide complex according to claim 1 which i H.

Detailed Description of the Invention

[0001]

[Field of the Invention] this invention relates to the new anthracycline-macrolide complex which makes it point to an anthracycline system antitumor antibiotic to lungs by using macrolides as medicine transport support.

[0002]

Description of the Prior Art

An anthracycline system antitumor antibiotic, for example, an adriamycin, is one of the anticancer agents currently used present most widely. However, while the antibiotic of this system has clear effectiveness on clinical, a difficulty is in a si effect, therefore the derivative of the masses aiming at mitigation of a side effect is compounded chiefly now. For examp while THP-adriamycin which one of this invention persons developed had the antitumor activity like the adriamycin, it mitigated and toxicity became slight [a side effect] (the trouble of a Tsukakoshi **:anticancer agent derivative development, cancer and the chemotherapy 15 (8), 2173-2178 (1988)).

[0003] If such actual condition is taken into consideration, while an anthracycline system antitumor antibiotic also includ the purpose of side-effect mitigation, it is known that it is the medicine which needs most an application of the medicine delivery technique aiming at an internal-organs inclination. For example, although it is invalid to the lung cancer, supposi a cause is in the directive badness to lungs and a medicine comes to be condensed by lungs, this becomes effective also i lung cancer and can expect mitigation of the side effect by reduction-izing of a required dosage simultaneously.

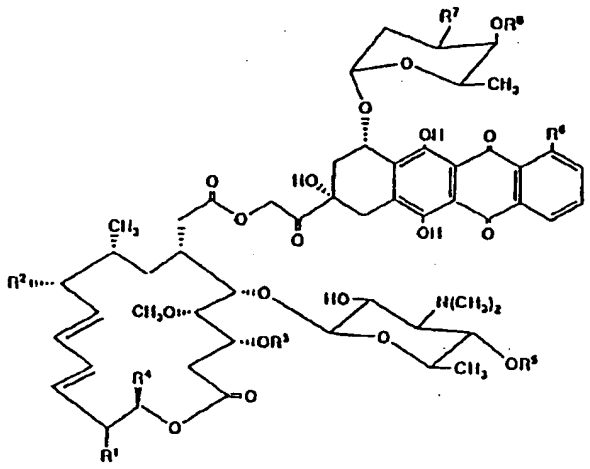
[0004] Having the compatibility with a macrolide antibiotic strong against specific internal organs, especially lungs is already known well. That is, generally a macrolide antibiotic is excellent in organization translatability, and shows good translatability like a quinolone antimicrobial to lungs (the 4th development of ******** (Hirokawa ******) 332 -335 pa (Heisei 3)).

TECHNICAL PROBLEM

Problem(s) to be Solved by the Invention

In view of the status of the above-mentioned conventional technique, it took up that this invention person made lungs poi to an anthracycline system antitumor antibiotic as a technical probrem which should be solved, and it tries to use the goo macrolide antibiotic of lung translatability for transportation support as this resolution means, and came to complete this invention.

[0006] this invention is explained below. this invention matter is the following formula (I).



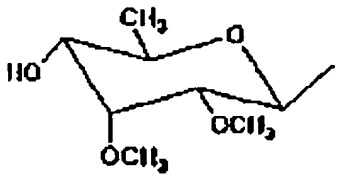
(I)

[0007]

[0008] It is alike and, therefore, is shown. The aglycon skeleton of the macrolide antibiotic which is a support fraction in this invention matter is 16 member ring -11, i.e., a 2-oxo ****** cyclohexa deca, and 13-diene, and the ****** nose is indispensable as sugar connected with the 6th place of this 16 member ring. The basic skeleton of the anthracycline syste antitumor antibiotic as a medicine fraction is 5 and 12-naphthacene ******, and the Dow-Jones ******** is indispensab as sugar connected with the 10th place of this naphthacene ******. The combination with a support fraction and a medici

[0010] [Formula 8]

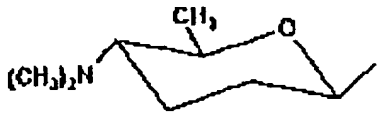
＊ ＊ [化8]



(II)

[0011] R^2 O=, HO, CH_3 COO. C_2H_5 COO, or $R^{10}O$ (however, R^{10} expresses the following formula (III)) is expressed.

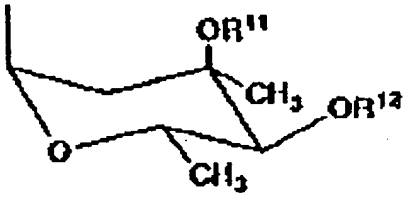
[0012] [Formula 9]



(III)

[0013] R^3 H and $COCH_3$ Or COC_2H_5 It expresses. R^4 CH_3 Or C_2H_5 It expresses. R^5 Micah Lowe's shown by H or the following formula (IV) is expressed, and it is

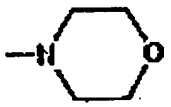
[0014] [Formula 10]



(IV)

[0015] However, the inside of a formula (IV) and R^{11} are H or $COCH_3$. It expresses and R^{12} is H, $COCH_3$, COC_2H_5, and COC_3H_7. Or $COCH_2CH_2(CH_3)_2$ It expresses. R^6 H. OH, or OCH_3 It expresses. R^7 NH_2 and $NHCOCF_3$ Or

[0016] [Formula 11]



[0017] ******. R^8 H or the following formula (V) is expressed.

[0018]

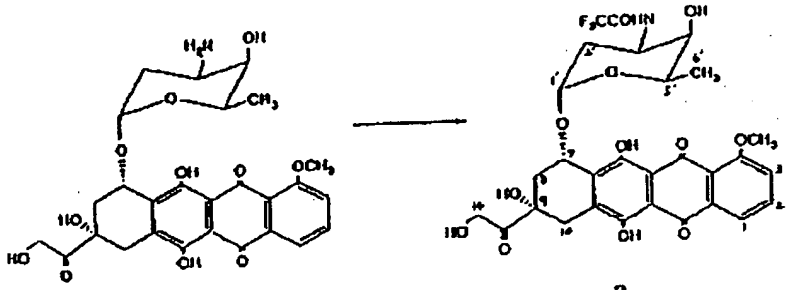
[Formula 12]

(V)

[0019] As an example of the macrolide antibiotic as a support fraction, ****** mycin, a leucomycin, ****** mycin, a kitasamycin, ****** mycin, a spiramycin, tylosin and these ester derivatives, and acid chloride can be mentioned.

[0020] As an example of the anthracycline system antitumor antibiotic as a medicine fraction, a daunorubicin, the doxorubicin (****** mycin), the ****** vicine (THP-adriamycin), ****** vicine, and these acid chloride can be

[0022]
[Effect of the Invention] It is expected that this invention matter (I) acts effectively to a lung cancer. That is, it is in viv though it is effective in the former to in vitro. The anthracycline system antitumor antibiotic which did not show [as opposed to / the lung cancer / then] Tsuguaki effectiveness comes to be condensed by the lung-cancer organization, and, a result, comes to demonstrate original effectiveness.
[0023] **[Example]** The example indicated below explains this invention still concretely.
[0024]
[Example 1]
[Formula 13]

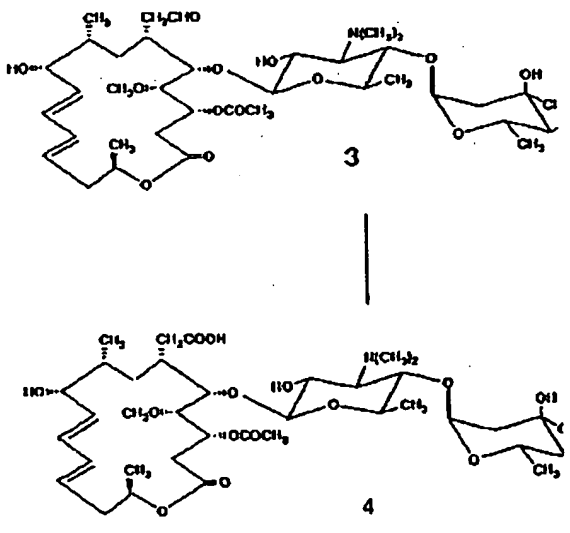


1 2

[0025] Raw material compound 1 Chloroform 9.00ml of an amount was made to suspend 600.0mg (1.035mmol) 15 times, cooled at 0°C, and triethylamine 144.3μl of a grade mol was added. Next, at 0 degree C, 3.00ml of the anhydrous trifluoroacetic acids of an amount was added 5 times, and it agitated for 3.5 hr. Methanol 5.00ml was added under [after checking an end of a reaction] ice-cooling with thin-layer chromatography (TLC) (chloroform:methanol =5:1), and vacuum concentration was carried out until it became sirupy. The concentration residue was melted in methanol 290ml, and, in addition, 6.42ml of 10%-potassium carbonate solutions of a 5 times mol was agitated under ice-cooling for 1.5 hr. Vacuum concentration of the system of reaction was carried out to about 150ml after checking an end of a reaction by TLC (chloroform:methanol =5:1), 500ml of water was added, and chloroform (80mlx3) performed the liquid separation extraction. Vacuum concentration of the organic layer was carried out, the silica gel chromatography (Daisogel, 33 g, and ethyl acetate) refined the concentration residue, and 560.0mg (84.6% of yield) of the low-red-heat crystals of the mark compound 2 (AD-N-TFA) was obtained.

[0026] Compound 2: $[\alpha]$ D^{34}+290.4° (c 1.50, MeOH)
^{1}H-NMR(CD_3OD, 270MHz):δ
1.28 (s, H-6')
1.78 (dd and H-2'a)
2.05 ~ 2.19 (m, H-2'b, H-8a)
2.35 (d, H-8b)
2.80, 2.99 (ABq, H-10a, H-10b)
3.67 (t like, H-4')
3.96 (s, OMe)
4.14 ~ 4.35 (m, H-3', H-5')
4.74 (s, H-14)
5.01 (dull d, H-7)
5.40 (d like, H-1')
7.43 (dd, H-3)
7.65 ~ 7.77 (m, H-1, and H-2)

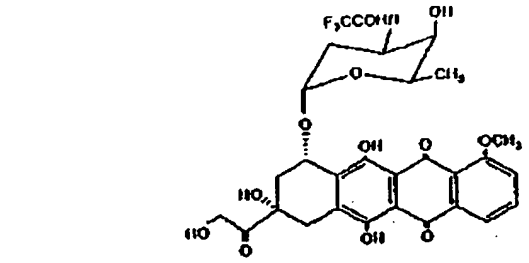
[0027]
[Formula 14]



3 4

vacuum concentration was carried out, the silica gel chromatography (Daisogel, 30 g, and chloroform:methanol =10:1) refined the concentration residue, and 510.5mg (82.0% of yield) of the white form-like solid-states of the mark compoun (18-COOH-****** mycin) was obtained.

[0029] [Formula 15]



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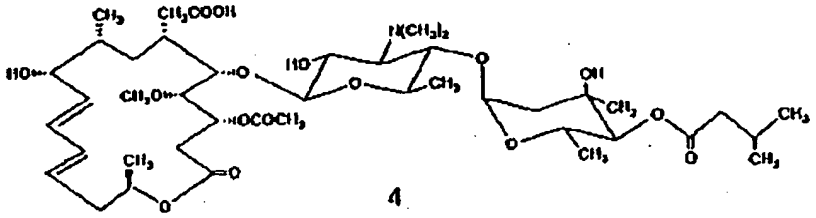

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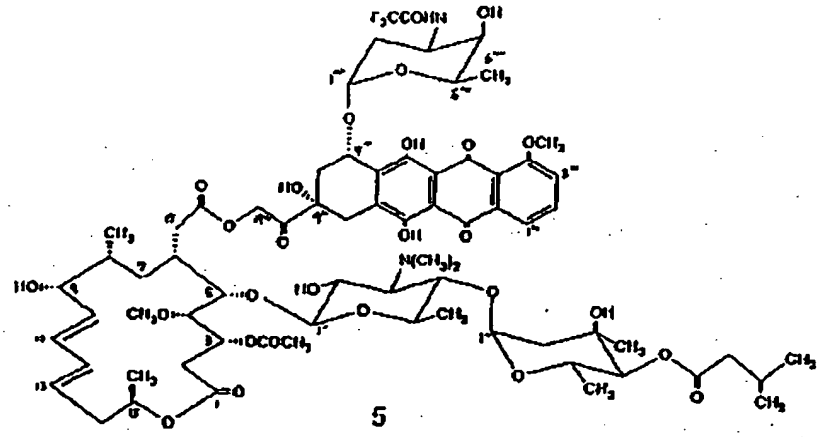
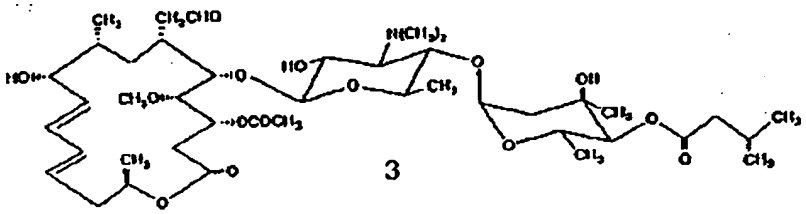


5

[0030] Compound 4 365.0mg (0.4325mmol) was melted in anhydrous tetrahydrofuran (THF) 3.65ml of an amount 10 x, alpha-naphthalene carbonyl chloride 68.4μl of a mol was added 1.05 times with triethylamine 90.5μl of a mol 1.5 times, and it agitated for 1 hour. a compound 4 -- receiving -- etc. -- compound 2 of a mol in 276.6mg, the amount of 10 x is anhydrous to a compound 2 -- what was melted in THF2.77ml was added to the system of reaction of a compound 4, 4-dimethylamino pyridine 105.7mg and anhydrous benzene 3.65 ml of 2 double mol were added, and it was made to react for 3 hr 10ml of water was added after checking -- 12g) After refining with ethyl acetate and acetic-acid acidity (pH3) and eluting the unreacted compound 2 etc., It eluted and refined by (chloroform:methanol =15:1) and 40.8mg (8.3% of yield) of the low-red-heat crystals of the mark compound 5 (18-(AD-N-TFA)-****** mycin) was obtained.

[0031] Compound 5:[alpha] D31+76.3 degree(c0.80 and CHCl3)
^{1}H-NMR($CDCl_3$,270MHz):delta
0.97 (d)
1.03 (d)

3.22 ~ 3.45 (m)
3.56 (s , OMe of 4)
3.60 ~ 3.69 (m)
4.00 (d)
4.09 (s, OMe of 4''')
4.42 (s, H-14''')
4.40 ~ 4.52 (m)
4.63 (d)
4.97 ~ 5.11 (m)
5.17 (d)
5.31 (dd, H-7'''')
5.53 (dd, H-1'''')
5.58 ~ 5.85 (m, H-12, 13)
6.07 (dd, H-10)
6.54 ~ 6.70 (m, H-11, NH)
7.40 (d, H-3''')
7.79 (t, H-2''')
8.06 (d, H-1''')
[0031]
[Example 2]
[0032]
[Formula 16]



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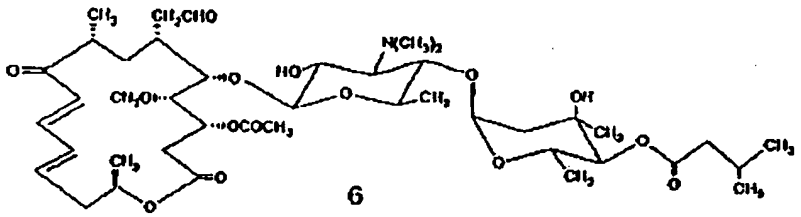

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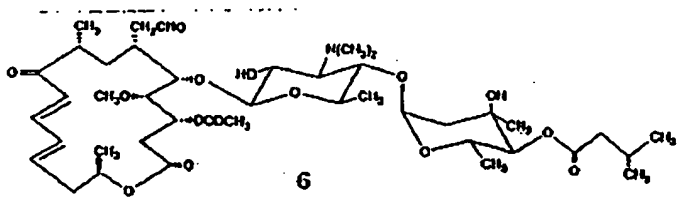
[0033] Raw material compound 3 141ml of 7.03g (8.48mmol) anhydrous methylene-chloride solutions was ****ed at the room temperature in the anhydrous methylene-chloride solution of 6.10g of the De Dis Martin reagents (14.4mmol), and they were agitated for 1.5 hr. the system of reaction -- ether 35.1ml and the saturation NaHCO3-Na2S2O3 (1:7) aqueous solution -- adding -- after a liquid separation extraction and an organic layer -- saturation sodium bicarbonate water -- subsequently vacuum concentration was washed and carried out with saturation brine The silica gel chromatography (Daisogel, 350 g, and chloroform:acetone =7:2) refined the concentration residue, and 5.00g (71.3% of yield) of the whit crystals of the mark compound 6 (carbomycin B) was obtained.
[0034]
[Formula 17]



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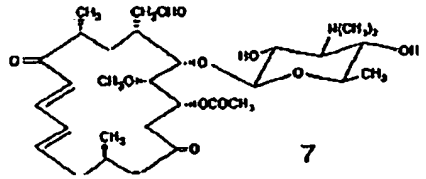

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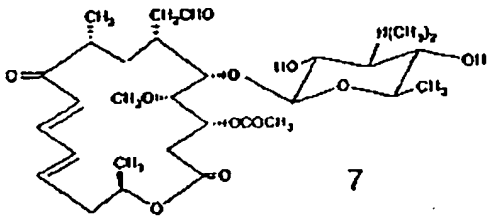
[Formula 18]



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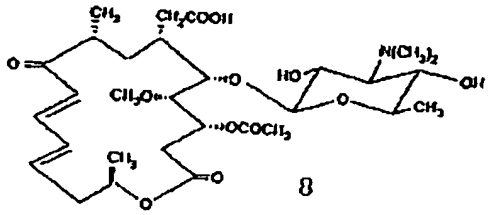
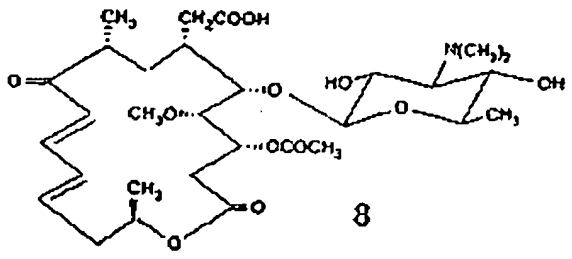


8

[0037] Compound 7 531.0mg (0.89mmol) was melted in dioxane 37ml and 16ml of water, 120.7mg (1.34mmol) of sodiu chlorites and 130.1mg (1.34mmol) of sulfamic acids were added at the room temperature, and it agitated for 30 minutes a the room temperature as it is. Saturation brine was added after the reaction end and chloroform extracted. Vacuum concentration of the organic layer is carried out, a silica gel chromatography (Dasigel, 28g, and chloroform:methanol =2: refines a residue, and it is the mark compound 8 of a white form-like solid-state. 418.7mg (0.68mmol) (77% of yield) wa obtained.

[0038] [Formula 19]



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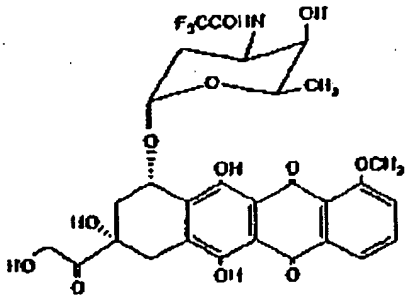

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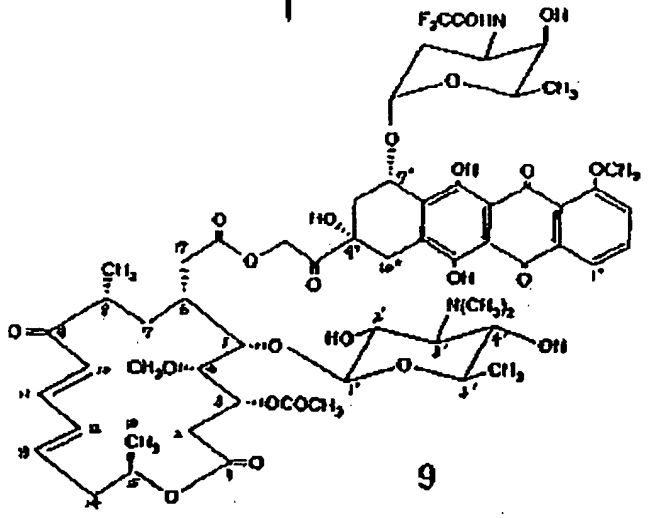


9

[0039] compound 8 the amount of 10 times is anhydrous in 385.0mg (0.6273mmol) -- after having melted in THF (3.85m having added alpha-naphthalene carbonyl chloride 99.3μl of a mol 1.05 times with triethylamine 131.2μl of a mol 1.5 ti and agitating for 40 minutes, anhydrous benzene 3.85ml was added

next, the compound 8 -- receiving -- etc. -- compound 2 of a mol in 401.2mg, the amount of 10 times is anhydrous to a compound 2 -- what was melted in THF -- the system of reaction of a compound 8 -- adding -- 4-dimethylamino pyridine 153.3mg of 2 double mol -- in addition, it was made to react for 3.5 hr 10ml of water was added after checking an end of a reaction by TLC (chloroform:methanol =5:1), and chloroform (50ml, 10mlx4) extracted. the concentration residue which carries out vacuum concentration and was obtained -- a silica gel chromatography (Daisogel -- 39mg) After ethyl acetate's refining and eluting the unreacted compound 2 etc., it is eluted by (n-butanol:ethanol:chloroform:H2 O=4:4:2:3). Furthermore, a silica gel chromatography (Kieselgel forflush, 25g, and chloroform:methanol =5:1) refines, and it is the mark compound 9 (78.5mg (10.1% of yield) of the low-red-heat crystals of 18- (AD-N-TFA-DMC) was obtained.).

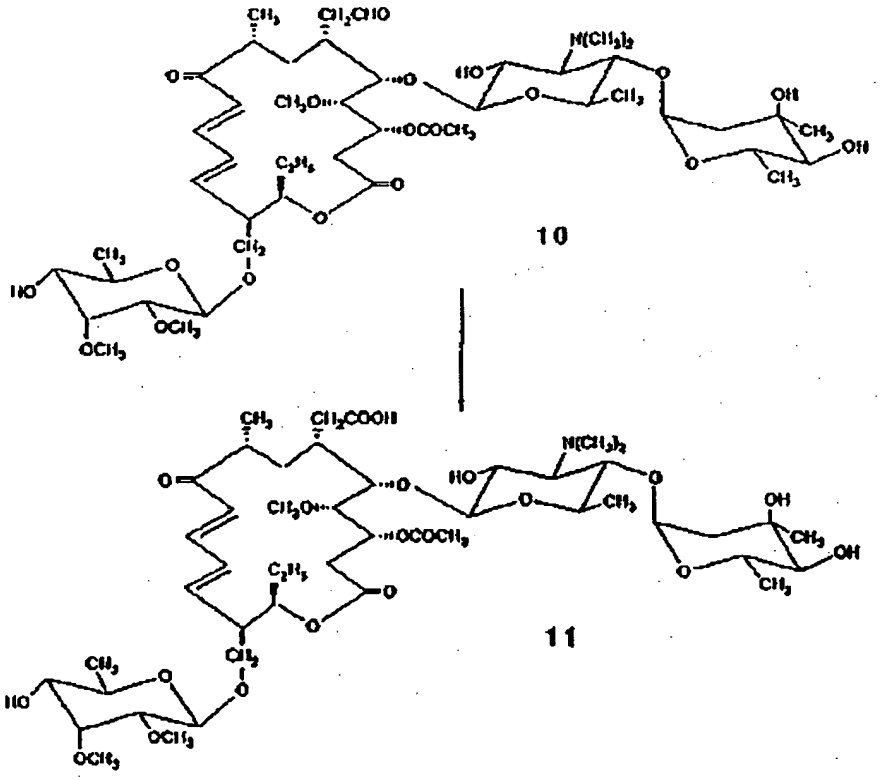
[0040] Compound 9:[alpha] D34+55.4 degree(cl.OO and CHCl3)
1H-NMR(CDCl3,270MHz):delta
1.06 -1.35(m)
2.13 (s and COCH3)
2.53 (sx2 and NMe2)
2.65 -3.40(m)
3.41 -3.75 --
3.56 (s --) Ome
3.58 (s and OMe)
4.09 (s --) Ome
4.35 -4.45 (m and H-14")
4.55 (d and H-1')
4.80 -4.94(m)
5.50 -5.40(m)
5.55 (dd and H-7")
6.00 -6.43 (m, H-10, 12, 13)
6.65 -6.78 (m and NH)
7.40 (d and H-1")
7.78 (t and H-2")
8.04(d and H-3")

[0041]

[Example 3]

[0042]

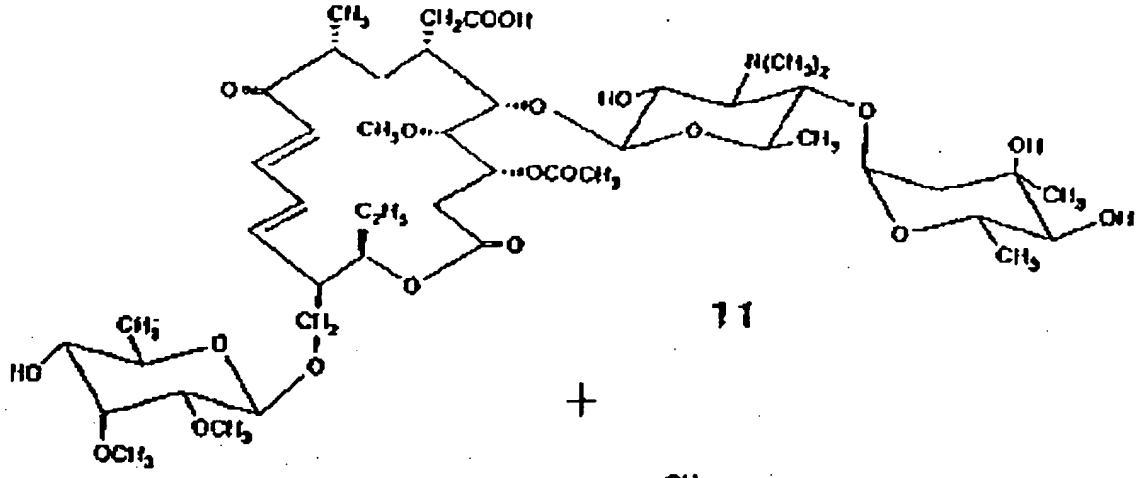
[Formula 20]



10

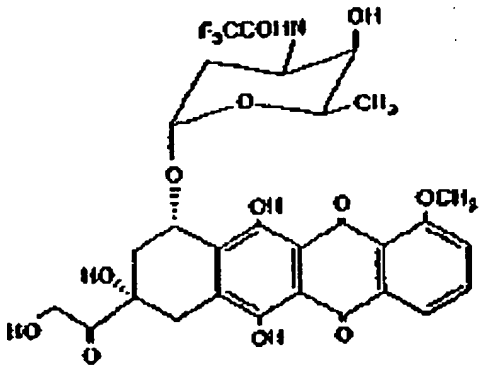
11

[0043] Raw material compound 10 (tylosin) 5.0g (5.46mmol) was melted in dioxane 350ml and 150ml of water, 1.23g of sodium chlorites (13.64mmol) and the sulfamic acid 1.38 (14.19mmol) were added at the room temperature, and it agitat at the room temperature as it is for 20 minutes. Saturation brine was added after the reaction end and chloroform extracte Vacuum concentration of the organic layer is carried out, a silica gel chromatography (Daisogel, 255g, chloroform:methanol =2:1) refines a residue, and it is the mark compound 11 of a white form-like solid-state. 3.73g (74 (4.00mmol) of yield) was obtained.

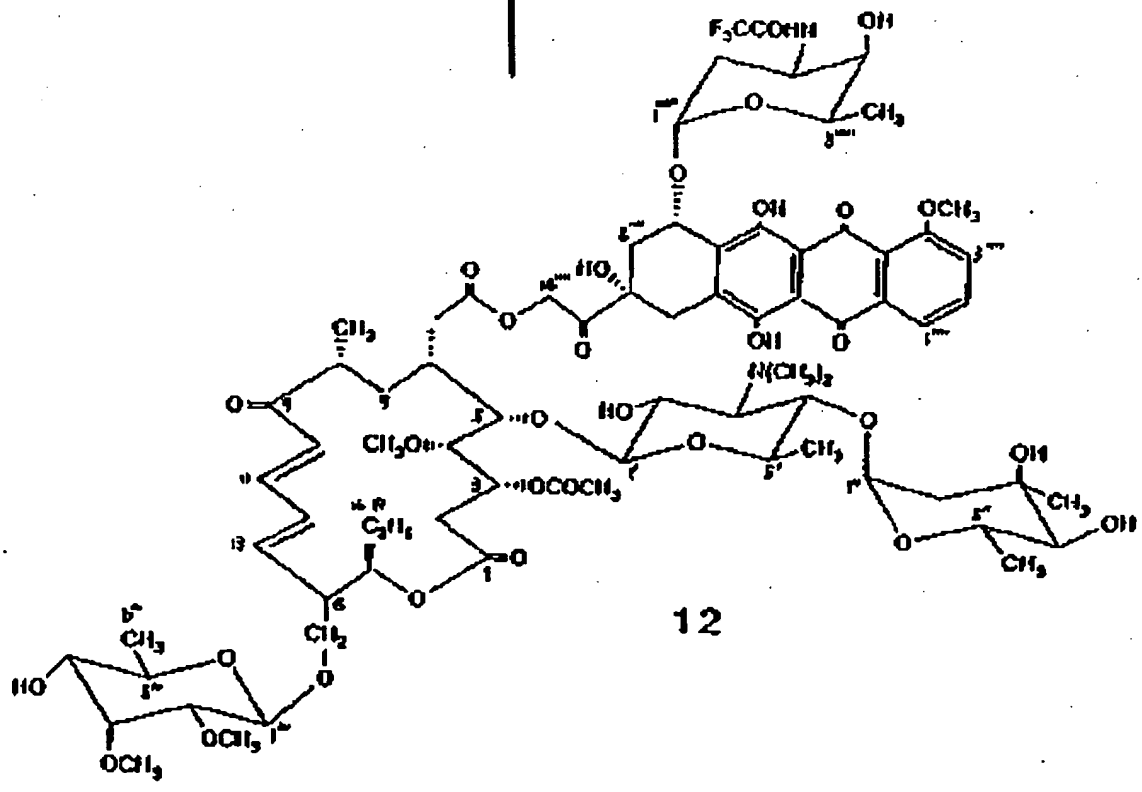


11

+



2



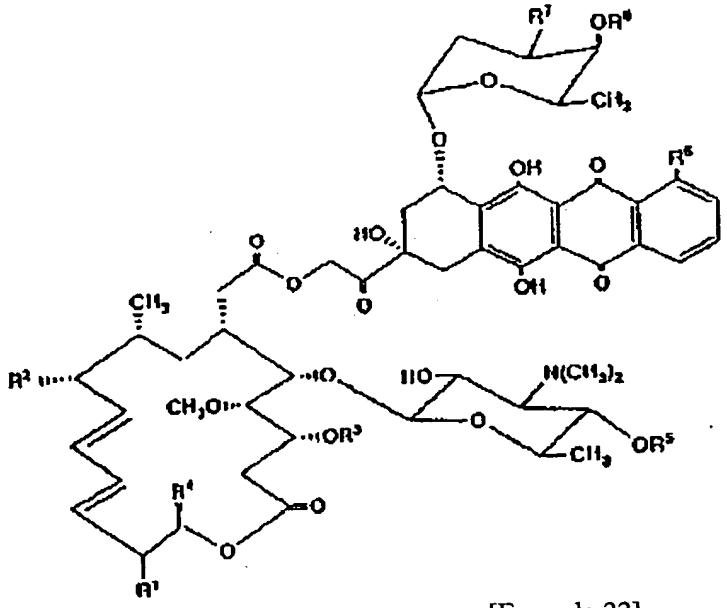
12

145g's, and ethyl acetate's) having refined the concentration residue which carries out vacuum concentration and was obtained and eluting the unreacted compound 2 etc., it eluted and refined by (chloroform:acetone =1:1) and 517.7mg (17.8% of yield) of the low-red-heat crystals of the mark compound 12 (20-(AD-N-TFA)-tylosin) was obtained.

[0046] 34+52.2 degrees () of Compound 12:[alpha] D [c] 1. OO and CHCl3

1H-NMR(CDCl3,270MHz):delta

0.94 (t and H-17)
1.00(d)
1.10 -1.40(m)
2.05(dd)
2.31(dd)
2.64 (s and NMe2)
2.90 -3.17(m)
3.48 (s and OMe)
3.61 (s --) Ome
3.76(s)
4.09 (s and OMe)
4.15 -4.38(m)
4.44-4.64(m)
4.47 (s and H-14"")
5.10 (dd and H-1") --
5.30 (m) --
5.53 () [dd and] [H-1] """
5.84 -6.00 (m and H-13)
6.15 -6.39 (m and H-10)
6.74 (d and NH)
7.35 (m and H-12)
7.40 (d and H-3"")
7.78 (t and H-2"")
8.03 (d and H-1"") --



(I)

[Formula 22]